ORIGINAL RESEARCH ARTICLE

Drug Safety 2001; 24 (2): 149-154
0114-5916/01/0002-0149/$22.00/0

Troglitazone and Liver Function Abnormalities

Lessons from a Prescription Event Monitoring Study and Spontaneous Reporting

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Abstract

Objectives: To investigate whether there were any cases of liver function abnormalities possibly associated with troglitazone use in general practice in England.

Design: A prescription-event monitoring (PEM) study was undertaken between October 1997 and December 1997.

Setting: Data from prescriptions were obtained electronically for the troglitazone cohort in the immediate postmarketing period.

Study Participants: Event data were obtained for a total of 1344 patients.

Results: Troglitazone was effective in 394 (75%) of the 529 patients for whom an opinion was given. The most frequent reasons for stopping treatment related to drug tolerability were malaise/lassitude (16 reports), abnormal liver function tests (11 reports) and nausea/vomiting (9 reports). The major cause of stopping troglitazone was because the drug was withdrawn from the market (1101 reports). 30 patients with liver dysfunction were identified from the cohort. In 9 of these patients there were alternative explanations for the liver dysfunction and hence these patients were not followed up further. 21 patients were followed up, for whom 19 questionnaires were returned. In 5 patients their liver dysfunction was assessed as possibly related to troglitazone, in 6 patients the liver dysfunction was unlikely to be attributed to troglitazone, while in 7 patients it was difficult to assess the causality because of limited information and confounding factors. The remaining patient was not included as this individual did not fit the inclusion criteria of the study.

Conclusion: Although the cohort is small (the drug was available for only 3 months in the UK), 5 patients with abnormal liver function, considered possibly related to troglitazone were detected in this PEM study. It is possible for PEM to contribute to the elucidation of safety signals in the UK.

Troglitazone is the first of a new group of orally active antidiabetic agents, the thiazolidinediones, and is indicated for the treatment of type 2 (non-insulin dependent) diabetes mellitus. Troglitazone acts primarily by enhancing the effects of insulin at peripheral target sites thereby increasing insulin sensitivity. It was launched in the UK in October 1997, then voluntarily withdrawn by the manufacturer in December 1997 in the UK, following reports of serious hepatic reactions in the US.[1] The product remained available in other markets for longer periods, but it was recently withdrawn in the US in March 2000.[2] While on the market in the US, the prescribing recommendations were to measure serum transaminase levels before therapy, then monthly during the first year of therapy. Thereafter, liver enzymes should be tested quarterly while receiving troglitazone therapy.[3]

The Drug Safety Research Unit (DSRU) aims to monitor the safety of new drugs intended for widespread use in general medical practice in England during the immediate postmarketing period. This study was undertaken to determine whether any of the patients in the prescription event monitoring (PEM) cohort had developed abnormal liver function related to troglitazone.

In this study we report the details of patients who developed abnormal liver function related to troglitazone, and relate our findings to spontaneous adverse reaction reports in the UK.

Method

An observational cohort study was undertaken using the technique of PEM. The exposure data were electronic records for troglitazone prescriptions issued by National Health Service doctors and general practitioners (GPs) dispensed in England during the collection period, which extended from October 1997 to December 1997. The Prescription Pricing Authority in England provided these prescriptions in confidence.

The outcome data were obtained by sending a simple questionnaire (called a 'green form') to the prescribing GP at least 6 months after the date of the first prescription for each individual patient. The green form requested information on the age and gender of the patient, indication for treatment, the start and stop dates of the treatment, the date and reason for stopping the drug if it had been stopped, an opinion about the effectiveness of the drug and all medical events that had occurred after troglitazone was prescribed. The term 'event' was defined as including any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any suspected drug reaction or any complaint considered of sufficient importance to enter into the patient's notes.[4]

All reported events were coded onto a computer using the DSRU dictionary which is arranged in a system-organ classification with specific 'lower' terms grouped together under broader 'higher' terms. These data were assembled for each patient to give the number of reports for each month following commencement of therapy.

At the end of the study the event data were scrutinised to ascertain whether there were reports of any hepatic abnormalities. The PEM database was searched for the terms hepatic failure, jaundice, hyperbilirubinaemia, hepatic tests, hepatic NOS (not otherwise specified), abnormal liver function tests and hepatitis, so that all events could be followed up. If sufficient information was already provided on the green form then the events were not followed up further. The green forms which did not contain sufficient information about the events were followed up by sending a simple questionnaire to the patient's GP. The questionnaire asked for any laboratory results of liver functions from 3 months before starting troglitazone, until 3 months after stopping the drug, information on other significant medical problems, concomitant medications during that period and also whether the GP thought that the hepatic dysfunction was related to troglitazone use or if there were any other possible explanations. If the patient developed liver function abnormalities more than 3 months after stopping troglitazone, then the details of the patient were not included in the analysis. Medically qualified staff assessed the causal relationship between

troglitazone and liver function abnormalities using the following principles. Assessment took account of whether the event was the reason for stopping therapy, concomitant medication, concurrent disorders, resolution or decrease in the levels of liver function abnormalities after withdrawal of troglitazone, previous history of similar problems or another specified cause and whether the GPs thought abnormal liver function tests to be attributable to troglitazone.

Deaths with no specified cause were followed up by obtaining death certificates from the Office for National Statistics in the UK.

The study was conducted in accordance with the International Ethical Guidelines for Biomedical Research prepared by the Council for International Organisations of Medical Sciences in collaboration with the World Health Organization.[5] The method also comprises with the guidelines on the Practice of Ethics Committees in Medical Research involving Human Subjects, as issued by the Royal College of Physicians of London.[6]

Results

2556 green forms were posted to 2034 GPs who had written prescriptions for troglitazone between October 1997 and December 1997. 1541 green forms were returned (60% response rate). 197 (12.8%) of the 1541 returned forms were classified as void [patient no longer registered with doctor (n = 87), troglitazone prescribed but not taken (4), no record of treatment in notes (37), blank forms (25) and duplicate green form for patient (1)]. Useful information that could be analysed was, therefore, available on 1344 patients.

529 (39%) of the green forms included an opinion about the effectiveness of troglitazone. Troglitazone was said to have been effective in 394 (75%) of the 529 patients for whom an opinion was given. The reason for stopping troglitazone was specified by the GPs for 1212 patients (90%) of the 1344 patients in the cohort. In the remaining 132 patients (10%) no reason for stopping troglitazone was specified. It should also be noted that some patients had more than one reason for stopping troglitazone (GPs reported 1265 reasons for stopping troglitazone in 1212 patients.) The most frequent reasons for stopping treatment with troglitazone were: drug withdrawn from the market (1101 reports; 80%); drug not effective (31 reports); and referred to hospital but reason not specified (22 reports). The other major causes of stopping treatment that were related to drug tolerability were malaise/lassitude (16 reports); abnormal liver function tests (11 reports); and nausea/vomiting (9 reports). The remaining 22 reports consisted of less than 5 reports for other minor events as the reason for stopping troglitazone.

There were 30 green forms containing 1 or more of the terms for liver dysfunction (2% of the evaluable forms). After carefully examining these 30 reports, 21 patients were followed up by sending a simple questionnaire to the GPs. For the other 9 patients there were other explanations for their liver dysfunction and they were not followed up further. Questionnaires for 19 of the 21 patients were returned.

After assessment, it was considered that 5 of the 19 patients for whom questionnaires were returned had liver dysfunction that was possibly related to troglitazone use. Of these 5 patients, 2 patients were reported by their GP as having experienced suspected adverse drug reactions to troglitazone, 1 of which was reported to the UK Committee on Safety of Medicines (CSM).

This patient was a 68-year-old woman, with a past history of type 2 diabetes mellitus and chronic leg ulceration. Three weeks after starting troglitazone, abnormal liver function was detected, with a bilirubin level of 11 mmol/L, an aspartate transaminase level 59 IU/L, a γ-glutamyl transferase level of 51 IU/L and an alkaline phosphatase level of 151 IU/L. Troglitazone was discontinued. The patient was also taking acarbose, glibencamide (glyburide), loratadine and a long acting insulin ('Mixtard' insulin, a combination of 30% regular human insulin and 70% neutral protamine Hagedorn human insulin) at the time of the event. The GP thought that the abnormal liver function was attributable to troglitazone and had reported it to the CSM.

Table I. Summary of information on the 5 patients who had possible troglitazone-related abnormal liver function

Patient	Age (y)/ gender	Time to detection	LFTs while receiving troglitazone (IU/L)	LFTs after stopping troglitazone (IU/L)[a]	Resolution of LFTs after stopping troglitazone	Causality
1	68/F	21 days	AST: 59 γ-GT: 51 ALP: 151	AST: 58 γ-GT: 52 ALP: 141	1 day	Possible (reported to the CSM)
2	62/M	11 days	AST: 55 γ-GT: 121 ALP: 664	AST: 14 γ-GT: 67 ALP: 302	7 days	Possible
3	45/F	4 days	ALP: 252	ALP: 229	20 days	Possible
4	75/F	71 days	AST: 112[b]	AST: 32	27 days	Possible
5	50/F	4 days	AST: 39 γ-GT: 253	AST: 32 γ-GT: 198	10 days	Possible (reported as an ADR)

a Reference range: ALT 1-45 IU/L; AST 1-36 IU/L; ALP 35-150 IU/L; γ-GT 5-40 IU/L.

b Value of liver enzyme recorded 1 month after stopping drug.

ADR = adverse drug reaction; **ALP** = alkaline phosphates; **ALT** = alanine amino transferase; **AST** = aspartate transaminase; **CSM** = UK Committee on Safety of Medicines; **F** = female; **γ-GT** = γ-glutamyl transferase; **LFTs** = liver function tests; **M** = male.

Table I summarises information on the 5 patients who had possible troglitazone-related abnormal liver function. None of the patients experienced severe liver abnormalities, in only 3 cases did certain individual liver enzymes reach 3 times the upper limit of the reference range.

In 6 of the 21 patients who were followed up, the liver dysfunction was considered unlikely to be attributable to troglitazone, while in 9 patients (including the 2 for whom the questionnaires were not returned), it was difficult to assess the causality because of limited information and other confounding factors (table II). The remaining patient was not included in the analysis, as the abnormal liver function tests were detected more than 3 months after stopping troglitazone and this patient did not satisfy the inclusion criteria of the study (table II).

The first 9 patients summarised in table II were those patients for whom questionnaires were not sent out because there was an alternative explanation for the liver dysfunction: malignancies (n = 3); history of alcohol abuse (2); viral hepatitis (2); liver functions raised prior to starting troglitazone (n = 1); and history of gall stones (1).

None of the 24 deaths reported in this study were considered to be attributable to troglitazone.

Discussion and Conclusion

The cohort for this study (1344) is small because of the short duration of the availability of the product on the UK market (PEM cohorts on average include 11 024 patients).[4] After the study was terminated and in the light of the information from spontaneous reports, the PEM cohort was scrutinised to ascertain any hepatic abnormalities. These findings indicate that using PEM it was possible to detect a safety signal that would be considered to be a weak safety signal which was not detected by spontaneous reporting in the UK, where a regulatory decision was based on spontaneous reports from other countries.[1]

The findings from this PEM study were not available at the time the decision was made. It is obvious that the quality of such public health decisions improves with more good quality and relevant information. Data from all appropriate sources should be available at the earliest possible opportunity. To achieve this there is a need to establish a pharmacovigilance network of units and organisations with pharmacovigilance research and monitoring capabilities to exchange information and integrate activities. Advances in information technology will increasingly make such integration more effective. With such a network in place it will be possible to

Table II. Summary of information on the patients who had liver function abnormalities that were thought to be unlikely to be related to troglitazone treatment or for who data was unassessable

Patient	Age (y)/ gender	Time to detection	LFTs while receiving troglitazone (IU/L)	LFTs after stopping troglitazone (IU/L)[a]	Resolution of LFTs after stopping troglitazone (IU/L)	Alternative explanation/ confounding factors	Causality
1	74/M		ALP level raised[b]	NS		Malignancy	Unlikely
2	91/M	25 days	LFTs raised[b]	NS		Liver secondary malignancies	Unlikely
3	66/M		Bilirubin level raised[b]	NS		Malignancy	Unlikely
4	57/M	21 days	Abnormal LFTs[b]	NS		History of alcoholism	Unlikely
5	73/M		γ-GT: 120	NS		History of alcoholism	Unlikely
6	58/F	3 days	Abnormal LFTs[b]	NS		Viral hepatitis	Unlikely
7		10 days	Bilirubin level raised[b]	NS		Viral Hepatitis	Unlikely
8	63/F		γ-GT level raised	NS		Pre-existing abnormal LFTs	Unlikely
9	55/F		Abnormal LFTs[b]	NS		History of gall stones	Unlikely
10	54/F	14 days	γ-GT: 95 ALP: 245	γ-GT: 69 ALP: 95	1 day	Fatty infiltration of liver	Unlikely (values again started to increase within a week)
11	72/M	14 days	ALT: 23	NS		CCF	Unlikely
12	52/F		γ-GT level raised[b]	NS		Other medication	Unlikely
13	73/M	20 days	γ-GT: 126	γ-GT: 148		History of alcoholism	Unlikely
14	51/M	72 days	ALT: 38 γ-GT: 88	NS		Hypercholesterolaemia	Unlikely
15	64/F	56 days	AST: 50 ALT: 83 γ-GT: 159 ALP: 232	AST: 19 ALT: 33 γ-GT: 109 ALP: 110	12 days	Viral arthropathy	Unassessable
16	61/M		LFTs slightly raised[b]	NS		Viral hepatitis	Unlikely
17	45/M	52 days	ALT: 23 Bilirubin: 18	NS		Jaundice	Unassessable
18	53/F		AST: 66	AST: 43			Unassessable
19	45/F	14 days	γ-GT: 99	NS			Unassessable

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conduct evaluation exercises similar to the one outlined here involving troglitazone, at an earlier stage in order to make them useful for public health.

Acknowledgements

The authors would like to thank all the general practitioners who diligently completed and returned their green forms. Without their co-operation this investigation would not have been possible.

The Drug Safety Research Unit (DSRU) is a registered charity, number 327206. It receives unconditional grants from a number of pharmaceutical companies. These companies have no say in the conduct of the studies and have no statistical or editorial control over analysis or reporting of results. The DSRU has received such funds from Glaxo Wellcome but there has been no external funding of the study reported in this paper.

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Table II. Contd

Patient	Age (y)/ gender	Time to detection	LFTs while receiving troglitazone (IU/L)	LFTs after stopping troglitazone (IU/L)[a]	Resolution of LFTs after stopping troglitazone (IU/L)	Alternative explanation/ confounding factors	Causality
20	76/F	4 days	ALP: 198	NS			Unassessable
21	47/M	35 days	Bilirubin: 20	NS			Unassessable
22	M		Abnormal LFTs[b]	NS		Questionnaire not returned	Unassessable
23	F		γ-GT level raised[b]	NS		Questionnaire not returned	Unassessable
24	57/F	5 months	ALT: 280 γ-GT: 320 ALP: 380	NS		Abnormal LFTs recorded 3 months after stopping drug	Did not fit inclusion criteria for the study
25	35/M	45 days	ALT: 127	NS			Unassessable

a Reference range: ALT 1-45 IU/L; AST 1-36 IU/L; ALP 35-150 IU/L; γ-GT 5-40 IU/L; bilirubin 3-17 mmol/L.

b Values of LFTs not specified and some instances no specific liver abnormality mentioned.

ALP = alkaline phosphates; **ALT** = alanine amino transferase; **AST** = aspartate transaminase; **CCF** = congestive cardiac failure; **CSM** = Committee on Safety of Medicines; **F** = female; **γ-GT** = γ-glutamyl transferase; **LFTs** = liver function tests; **M** = male; **NS** = not specified.